

WHAT IS CLAIMED IS:

- 1 1. A leptin receptor (OB-R) polypeptide.
- 1 2. The leptin receptor of claim 1 characterized by
  - 2 a) specific binding to leptin under physiological conditions;
  - 3 b) expression at high levels in cells of the hypothalamus, and expression at
  - 4 lower levels in adipose tissue, testes, heart, and brain; and
  - 5 c) having sequence similarity to gp130 cytokine receptors.
- 1 3. The leptin receptor of claim 1 which is encoded by a nucleic acid which is
  - 2 identifiable with a polymerase chain reaction (PCR) probe selected from group consisting
  - 3 of a probe for clone 7 (forward primer SEQ ID NO:42 and reverse primer SEQ ID
  - 4 NO:43), a probe for clone 11 (forward primer SEQ ID NO:44 and reverse primer SEQ
  - 5 ID NO:45), and both clone 7 and clone 11.
- 1 4. The leptin receptor of claim 3, which is encoded by a nucleic acid which is
  - 2 identifiable with a PCR probe selected from the group consisting of a probe for clone 42
  - 3 (forward primer SEQ ID NO:26 and reverse primer SEQ ID NO:46); a probe for clone
  - 4 46 (forward primer SEQ ID NO:47 and reverse primer SEQ ID NO:48); a probe for
  - 5 clone 58 (forward primer SEQ ID NO:47 and reverse primer SEQ ID NO:50); a probe
  - 6 for clone S14 (forward primer SEQ ID NO:51 and reverse primer SEQ ID NO:52); and a
  - 7 probe for clone S3 (forward primer SEQ ID NO:53 and reverse primer SEQ ID NO:54).
- 1 5. The leptin receptor of claim 1 which is selected from the group consisting of OB-
  - 2 Ra, OB-Rb, OB-Rc, OB-Rd, and OB-Re, or allelic variants thereof.
- 1 6. The leptin receptor of claim 1 which is selected from the group consisting of:
  - 2 a) N-terminal corresponding to OB-Ra through Lys<sup>889</sup> and C-terminal
  - 3 corresponding to a C-terminal selected from the group consisting of OB-Rb, OB-
  - 4 Rc, and OB-Rd after Lys<sup>889</sup>;
  - 5 b) N-terminal corresponding to OB-Rb or OB-Rc through Lys<sup>889</sup>, and C-
  - 6 terminal corresponding to OB-Ra or OB-Rd after Lys<sup>889</sup>;

- 7 c) N-terminal corresponding to OB-Rd through Lys<sup>889</sup>, and C-terminal
- 8 corresponding to OB-Ra, OB-Rb, or OB-Rc;
- 9 d) N-terminal corresponding to OB-R from Pro<sup>664</sup> to Lys<sup>889</sup>, and C-terminal
- 10 corresponding to OB-Ra, OB-Rb, OB-Rc, and OB-Rd;
- 11 e) N-terminal corresponding to OB-R from Met<sup>733</sup> to Lys<sup>889</sup>, and C-terminal
- 12 corresponding to OB-Ra, OB-Rb, OB-Rc, and OB-Rd;
- 13 f) N-terminal selected from the group consisting of OB-Ra, OB-Rb, OB-Rd,
- 14 and OB-R from Pro<sup>664</sup>, to His<sup>796</sup>, and OB-Re from His<sup>796</sup>;
- 15 g) N-terminal corresponding to OB-R from Met<sup>733</sup> to His<sup>796</sup>, and OB-Re from
- 16 His<sup>796</sup>, or allelic variants thereof.

- 1 7. The leptin receptor of claim 1 wherein
- 2 a) the N-terminal sequence is selected from the group consisting of
- 3 i) amino acid residues 1-889;
- 4 ii) amino acid residues 23-889;
- 5 iii) amino acid residues 28-889;
- 6 iv) amino acid residues 133-889;
- 7 v) amino acid residues 733-889;
- 8 vi) amino acid residues 1-796;
- 9 vii) amino acid residues 23-796;
- 10 viii) amino acid residues 28-796;
- 11 ix) amino acid residues 133-796; and
- 12 x) amino acid residues 733-796; and
- 13 b) the C-terminal sequence is selected from the group consisting of
- 14 i) SEQ ID NO:11;
- 15 ii) SEQ ID NO:12;
- 16 iii) SEQ ID NO:13;
- 17 iv) SEQ ID NO:14; and
- 18 v) SEQ ID NO:15;
- 19 wherein the numbering is based on the amino acid sequence of the full length transcribed
- 20 murine leptin receptor, including the signal peptide, or allelic variants thereof.

- 1 8. The leptin receptor of claim 1 which is a soluble receptor.

1 9. The leptin receptor of claim 8 which is selected from the group consisting of  
 2 a) OB-Re;  
 3 b) an N-terminal sequence which selected from the group consisting of OB-  
 4 Ra, OB-Rb, OB-Rd, and OB-R from Pro<sup>664</sup>, through His<sup>796</sup>, and a C-terminal  
 5 sequence which is OB-Re from His<sup>796</sup>;  
 6 c) an N-terminal sequence which is selected from the group consisting of  
 7 i) amino acid residues 1-796;  
 8 ii) amino acid residues 23-796;  
 9 iii) amino acid residues 28-796;  
 10 iv) amino acid residues 28-796 preceded by an N-terminal Asp-Pro  
 11 dipeptide;  
 12 v) amino acid residues 133-796; and  
 13 vi) amino acid residues 733-796; and  
 14 a C-terminal sequence which is SEQ ID NO:15 after His<sup>796</sup>;  
 15 d) a sequence selected from the group consisting of  
 16 i) Asp-Arg-Trp-Gly-Ser-Tyr<sup>420</sup> (SEQ ID NO:77) → Pro<sup>641</sup>;  
 17 ii) Asp-Arg-Trp-Gly-Ser-Ser<sup>118</sup> (SEQ ID NO:78) → Pro<sup>641</sup>;  
 18 iii) Asp-Arg-Trp-Gly-Ser-Leu<sup>123</sup> (SEQ ID NO:79) → Val<sup>331</sup>; and  
 19 e) any of the foregoing peptides in which a cysteine is substituted with an  
 20 amino acid selected from the group consisting of serine, threonine, and alanine;  
 21 wherein the numbering is based on the amino acid sequence of the full length transcribed  
 22 murine leptin receptor, including the signal peptide, or allelic variants thereof.

1 10. The leptin receptor of claim 1 which comprises a transmembrane domain, and is  
 2 an integral membrane protein.

1 11. The leptin receptor of claim 10 which further comprises a JAK binding motif  
 2 selected from "Box 1," "Box 2," and "Box 1" and "Box 2", which motif is downstream of  
 3 the transmembrane domain.

1 12. The leptin receptor of claim 1 which is a human leptin receptor.

1 13. The leptin receptor of claim 1 which is a murine leptin receptor.

1 14. The leptin receptor of claim 12 comprising an amino acid substitution selected  
2 from the group consisting of: Phe for Ser<sup>36</sup>; Asp for Tyr<sup>44</sup>; Ser for Leu<sup>49</sup>; Pro for Ser<sup>54</sup>;  
3 Leu for Ser<sup>60</sup>; Ala for His<sup>63</sup>; Ala for Thr<sup>66</sup>; Ala for Pro<sup>70</sup>; Ile for Thr<sup>77</sup>; Tyr for His<sup>78</sup>; Pro  
4 for Ser<sup>80</sup>; Gly for Arg<sup>92</sup>; Gly for Asp<sup>96</sup>; Thr for Ala<sup>103</sup> or Ile<sup>106</sup>; Ser for Leu<sup>118</sup>; Gly for  
5 Asp<sup>124</sup>; Thr for Lys<sup>138</sup>; Pro for Ser<sup>146</sup>; Asp for Val<sup>164</sup>; Leu for Gln<sup>177</sup>; Asp for Gly<sup>179</sup>; Gly  
6 for Glu<sup>192</sup>; deletion for Cys<sup>193</sup>; His for Leu<sup>197</sup>; Ser for Ile<sup>221</sup>; Leu for Asn<sup>233</sup>; Leu for Ser<sup>273</sup>;  
7 deletion for Thr<sup>278</sup>; Ala for Asp<sup>285</sup>; Glu for Lys<sup>286</sup>; Ser for Gly<sup>310</sup>; Arg for Met<sup>370</sup>; Ile for  
8 Ser<sup>379</sup>; Ser for Phe<sup>394</sup>; Ala for Glu<sup>417</sup>; Gly for Glu<sup>459</sup>; Ser for Ile<sup>476</sup>; Thr for Ile<sup>482</sup>; Thr for  
9 Ile<sup>551</sup>; His for Tyr<sup>586</sup>; Lys for Ile<sup>648</sup>; Ala for Ser<sup>686</sup>; His for Cys<sup>687</sup>; Thr for Ile<sup>759</sup>; Ile for  
10 Asn<sup>776</sup>; Asp for Gly<sup>781</sup>; Gly for Glu<sup>782</sup>; Gly for Ser<sup>827</sup>; Ala for Asp<sup>832</sup>; Arg for Pro<sup>892</sup>; Thr  
11 for Glu<sup>893</sup>; Asp for Thr<sup>894</sup>; or Leu for Glu<sup>896</sup>, wherein the numbering of the amino acids  
12 corresponds to the numbering adopted for the human leptin receptor, including the signal  
13 sequence.

1 15. An antigenic fragment of the leptin receptor of claim 1.

1 16. The antigenic fragment of claim 15 which is selected from the group consisting of  
2 SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34; and a sequence from about amino acid  
3 420 to about amino acid 621 of SEQ ID NO:10.

1 17. A derivative of the leptin receptor of claim 8 or 9 attached to a chemical moiety.

1 18. The derivative of claim 15 wherein the chemical moiety is a water-soluble  
2 polymer.

1 19. The derivative of claim 16 wherein the water soluble polymer is polyethylene  
2 glycol.

1 20. An isolated nucleic acid encoding a leptin receptor of claim 1.

1 21. An isolated nucleic acid encoding a leptin receptor of claim 5, 6, or 7.

1 22. An isolated nucleic acid encoding a leptin receptor of claim 8 or 9.

1 23. An isolated nucleic acid encoding a leptin receptor of claim 10 or 11.

1 24. An isolated DNA molecule encoding on expression a leptin receptor polypeptide  
2 selected from the group consisting of:

- 3 a) a polypeptide coding sequence of a DNA molecule of SEQ ID NO:1, 3, 5,  
4 7, or 9;
- 5 b) a DNA molecule complementary to the DNA molecule defined in (a);
- 6 c) a DNA molecule which hybridizes to the DNA molecule of (a) or (b), or a  
7 hybridizable fragment thereof;
- 8 d) a DNA molecule which is identifiable with a polymerase chain reaction  
9 (PCR) probe selected from group consisting of a probe for clone 7 (forward primer  
10 SEQ ID NO:42 and reverse primer SEQ ID NO:43), a probe for clone 11  
11 (forward primer SEQ ID NO:44 and reverse primer SEQ ID NO:45), and both  
12 clone 7 and clone 11; and
- 13 e) a DNA molecule that codes on expression for the polypeptide encoded by  
14 any of the foregoing DNA molecules.

1 25. The DNA molecule of claim 24 which is human.

1 26. The DNA molecule of claim 24 which is murine.

1 27. The DNA molecule of claim 24 which codes on expression for a polypeptide  
2 selected from the group consisting of:

- 3 a) a leptin receptor selected from the group consisting of OB-Ra, OB-Rb,  
4 OB-Rc, OB-Rd, and OB-Re, or allelic variants thereof;
- 5 b) a leptin receptor selected from the group consisting of:
- 6 i) N-terminal corresponding to OB-Ra through Lys<sup>889</sup> and C-terminal  
7 corresponding to a C-terminal selected from the group consisting of OB-  
8 Rb, OB-Rc, and OB-Rd after Lys<sup>889</sup>;
- 9 ii) N-terminal corresponding to OB-Rb or OB-Rc through Lys<sup>889</sup>, and  
10 C-terminal corresponding to OB-Ra or OB-Rd after Lys<sup>889</sup>;
- 11 iii) N-terminal corresponding to OB-Rd through Lys<sup>889</sup>, and C-terminal  
12 corresponding to OB-Ra, OB-Rb, or OB-Rc;

- 13 iv) N-terminal corresponding to OB-R from Pro<sup>664</sup> to Lys<sup>889</sup>, and C-  
 14 terminal corresponding to OB-Ra, OB-Rb, OB-Rc, and OB-Rd;  
 15 v) N-terminal corresponding to OB-R from Met<sup>733</sup> to Lys<sup>889</sup>, and C-  
 16 terminal corresponding to OB-Ra, OB-Rb, OB-Rc, and OB-Rd;  
 17 vi) N-terminal selected from the group consisting of OB-Ra, OB-Rb,  
 18 OB-Rd, and OB-R from Pro<sup>664</sup>, through His<sup>796</sup>, and OB-Re from His<sup>796</sup>,  
 19 and  
 20 vii) N-terminal corresponding to OB-R from Met<sup>733</sup> to His<sup>796</sup>, and OB-  
 21 Re from His<sup>796</sup>,  
 22 or allelic variants thereof;
- 23 c) a leptin receptor wherein
- 24 i) the N-terminal sequence is selected from the group consisting of
- 25 (1) amino acid residues 1-889;  
 26 (2) amino acid residues 23-889;  
 27 (3) amino acid residues 28-889;  
 28 (4) amino acid residues 133-889;  
 29 (5) amino acid residues 733-889;  
 30 (6) amino acid residues 1-796;  
 31 (7) amino acid residues 23-796;  
 32 (8) amino acid residues 28-796;  
 33 (9) amino acid residues 28-796 preceded by an N-terminal  
 34 Asp-Pro dipeptide;  
 35 (10) amino acid residues 133-796; and  
 36 (11) amino acid residues 733-796; and
- 37 ii) the C-terminal sequence is selected from the group consisting of
- 38 (1) SEQ ID NO:11;  
 39 (2) SEQ ID NO:12;  
 40 (3) SEQ ID NO:13;  
 41 (4) SEQ ID NO:14; and  
 42 (5) SEQ ID NO:15 after His<sup>796</sup>;
- 43 d) a leptin receptor having an amino acid sequence selected from the group  
 44 consisting of
- 45 i) Asp-Arg-Trp-Gly-Ser-Tyr<sup>420</sup> (SEQ ID NO:77) → Pro<sup>641</sup>;  
 46 ii) Asp-Arg-Trp-Gly-Ser-Ser<sup>118</sup> (SEQ ID NO:78) → Pro<sup>641</sup>;

47                   iii)    Asp-Arg-Trp-Gly-Ser-Leu<sup>123</sup> (SEQ ID NO:79) → Val<sup>331</sup>; and  
 48           e)       a leptin receptor as described in (a)-(d) above in which a cysteine is  
 49           substituted with an amino acid selected from the group consisting of serine,  
 50           threonine, and alanine;  
 51           wherein the numbering is based on the amino acid sequence of the full length  
 52           transcribed murine leptin receptor, including the signal peptide, or allelic variants  
 53           thereof.

1   28.    A nucleic acid molecule having a nucleotide sequence corresponding or  
 2   complementary to the DNA sequence set forth in SEQ ID NO:1, 3, 5, 7 or 9.

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1   29.    An oligonucleotide hybridizable under stringent conditions to the nucleic acid  
 2   molecule of claim 24.

1   30.    An oligonucleotide hybridizable under stringent conditions to the nucleic acid  
 2   molecule of claim 27.

1   31.    An oligonucleotide hybridizable under stringent conditions to the nucleic acid  
 2   molecule of claim 28.

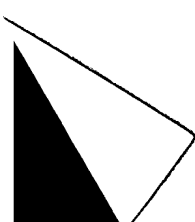
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1   32.    The oligonucleotide of claim 29, 30, or 31 selected from the group consisting of  
 2   SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ  
 3   ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID  
 4   NO:30, SEQ ID NO:31, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID  
 5   NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID  
 6   NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID  
 7   NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID  
 8   NO:53, and SEQ ID NO:54.

1   33.    The oligonucleotide of claim 32 which is labeled.

1   34.    The nucleic acid of claim 20, 21, 22, or 23 which is DNA.

1   35.    A vector comprising the DNA of claim 34.



- 1 36. A vector comprising the DNA of claim 24, 27, or 28.
- 1 37. An expression vector which comprises the DNA of claim 34, operatively  
2 associated with an expression control sequence.
- 1 38. An expression vector which comprises the DNA of claim 24, 27, or 28,  
2 operatively associated with an expression control sequence.
- 1 39. An unicellular host transformed or transfected with a DNA molecule of claim 34.
- 1 40. An unicellular host transformed or transfected with a DNA molecule of claim 24,  
2 27, or 28.
- 1 41. An unicellular host transformed or transfected with an expression vector of claim  
2 37.
- 1 42. An unicellular host transformed or transfected with an expression vector of claim  
2 38.
- 1 43. The unicellular host of claim 41 selected from the group consisting of bacteria,  
2 yeast, mammalian cells, plant cells, and insect cells, in tissue culture.
- 1 44. The unicellular host of claim 42 selected from the group consisting of bacteria,  
2 yeast, mammalian cells, plant cells, and insect cells, in tissue culture.
- 1 45. The unicellular host of claim 43, wherein the unicellular host is selected from the  
2 group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*, *Saccharomyces*, *Pichia*,  
3 *Candida*, *Hansenula*, *Torulopsis*, CHO, R1.1, B-W, LM, COS 1, COS 7, BSC1, BSC40,  
4 BMT10, and Sf9 cells.
- 1 46. The unicellular host of claim 44, wherein the unicellular host is selected from the  
2 group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*, *Saccharomyces*, *Pichia*,  
3 *Candida*, *Hansenula*, *Torulopsis*, CHO, R1.1, B-W, LM, COS 1, COS 7, BSC1, BSC40,  
4 BMT10, and Sf9 cells.



- 1 47. A method for preparing a leptin receptor polypeptide comprising:  
2 a) culturing a cell according to any claim 43 under conditions that provide  
3 for expression of the leptin receptor polypeptide; and  
4 b) recovering the expressed polypeptide.
- 1 48. A method for preparing a leptin receptor polypeptide comprising:  
2 a) culturing a cell according to any claim 44 under conditions that provide  
3 for expression of the leptin receptor polypeptide; and  
4 b) recovering the expressed polypeptide.
- 1 49. The oligonucleotide of claim 29, 30, or 31 which is an antisense nucleic acid that  
2 hybridizes with an mRNA encoding leptin receptor.
- 1 50. A ribozyme which cleaves an mRNA encoding a leptin receptor.
- 1 51. A transgenic vector comprising a DNA molecule of claim 34.
- 1 52. A transgenic vector comprising a DNA molecule of claim 24, 27, or 28.
- 1 53. An antibody specific for a leptin receptor of claim 1.
- 1 54. An antibody according to claim 53 which is a monoclonal or polyclonal antibody.
- 1 55. An antibody according to claim 53 labeled with a detectable label.
- 1 56. An immortal cell line that produces a monoclonal antibody according to claim 54.
- 1 57. A method for preparing an antibody specific for a leptin receptor, comprising:  
2 a) immunizing a host animal with the leptin receptor of claim 1 admixed with  
3 an adjuvant; and  
4 b) obtaining antibody from the immunized host animal.
- 1 58. A method for preparing an antibody specific for a leptin receptor, comprising:

- 2 a) conjugating a peptide having a sequence selected from the group consisting
- 3 of SEQ ID NO:32, SEQ ID NO:33, and SEQ ID NO:34 to a carrier protein;
- 4 b) immunizing a host animal with the peptide-carrier protein conjugate of step
- 5 (a) admixed with an adjuvant; and
- 6 c) obtaining antibody from the immunized host animal.

1 59. A method for measuring the presence of a leptin receptor in a sample, comprising:

- 2 a) contacting a sample suspected of containing a leptin receptor with an
- 3 antibody that specifically binds to the leptin receptor under conditions which allow
- 4 for the formation of reaction complexes comprising the antibody and the leptin
- 5 receptor; and
- 6 b) detecting the formation of reaction complexes comprising the antibody and
- 7 leptin receptor in the sample,

8 wherein detection of the formation of reaction complexes indicates the presence of leptin

9 receptor in the sample.

1 60. The method according to claim 59 wherein the antibody is bound to a solid phase

2 support.

1 61. An *in vitro* method for evaluating the level of leptin receptor in a biological sample

2 comprising:

- 3 a) detecting the formation of reaction complexes in a biological sample
- 4 according to the method of claim 59 or 60; and
- 5 b) evaluating the amount of reaction complexes formed, which amount of
- 6 reaction complexes corresponds to the level of leptin receptor in the biological
- 7 sample.

1 62. An *in vitro* method for detecting or diagnosing the presence of a disease associated

2 with elevated or decreased levels of leptin receptor in a subject comprising:

- 3 a) evaluating the level of leptin receptor in a biological sample from a subject
- 4 according to claim 61; and
- 5 b) comparing the level detected in step (a) to a level of leptin receptor present
- 6 in normal subjects or in the subject at an earlier time,

7 wherein an increase in the level of leptin receptor as compared to normal levels indicates a  
8 disease associated with elevated levels of leptin receptor, and decreased level of leptin  
9 receptor as compared to normal levels indicates a disease associated with decreased levels  
10 of leptin receptor.

1 63. A pharmaceutical composition comprising a soluble leptin receptor according to  
2 any of claims 8 or 9, and a pharmaceutically acceptable carrier.

1 64. A method for treating obesity in a subject comprising administering a  
2 therapeutically effective amount of the pharmaceutical composition of claim 63.

1 65. The method according to claim 64, further comprising administering a treatment  
2 for diabetes, high blood pressure, and high cholesterol.

1 66. A body appearance improving cosmetic composition for reducing the body weight  
2 of an individual comprising a soluble leptin receptor of claim 8 or 9, and an acceptable  
3 carrier.

Add  
A' →

add B1